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DUNSTON, JENNIFER ANN	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

CONTINUATION SHEET

With respect to the rejection of claims 31-36 under 35 U.S.C. 103(a) as being unpatentable over Felgner et al in view of Zhou et al, Adema et al, Nagata et al, and Fomsgaard et al, Applicant's arguments filed 4/20/2009 have been fully considered but they are not persuasive.

The response asserts that the crux of the rejection relies upon Nagata and Fomsgaard as evidence of motivation to enrich GC content and as providing an expectation of higher expression of mRNA and improved immunogenicity. The response asserts that neither of the references relates to human tumor antigens and both expressly relate to expression of non-human genes in human cells. The response asserts that there is a distinct technical problem from the utility addressed by the present invention (expression of human tumor antigens in human cells *in vivo* to provide an immune response in a human host). Further, the response asserts that the primary references, which are considered as Felgner, Zhou and Adema, are not properly combinable with the secondary references of Nagata and Fomsgaard, because the primary references do not suggest modified mRNA which is GC enriched, and the secondary references are unrelated to anti-tumor therapy. Moreover, the response cites passages from pages 8, 13 and of the prior Office action. The remarks regarding these passages have been fully considered.

These arguments are not found persuasive. "A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton" *KSR*, 550 U.S. 398, 127 S. Ct. 1727, 82 USPQ2d 1385 at 1397. "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id*. Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would

employ." *Id.* at 398, 127 S. Ct. 1727, 82 USPQ2d at 1396. Because Felgner et al, Zhou et al, and Adema et al are all directed to a pharmaceutical composition for expression of a tumor antigen in a human, and Nagata et al and Fomsgaard et al are directed to codon optimization of a sequence for expression in a human, it would have been within the ordinary skill of the art to apply the codon optimization to a human sequence. A person of ordinary skill in the art would have readily recognized the benefit of optimizing the codons of any sequence for expression in a human cell regardless of the origin of the sequence (e.g., human, mouse, cow, bacteria, virus, etc.). One would have been motivated to make such a modification to improve the expression of the protein and reduce ribosomal pausing (e.g., Fomsgaard et al, page 1, lines 30-33).

The response comments on pages 16-17 of the prior Office action. The response asserts that expression *in vitro* does not correlate to expression *in vivo*. The response cites the Robinson reference provided with the response to the final Office action, which states "Our experiments were based upon overexpression by transient transfection, and *in vitro* translation. The extent to which codon bias influences gene expression *in vivo* remains an open question." This argument is not found persuasive. Applicant has not provided objective evidence that *in vitro* expression does not correlate with *in vivo* expression. Even if *in vivo* expression was unpredictable, the evidence cited in the rejection of record demonstrates the predictable expression of gp100 melanoma tumor antigen *in vivo* (Zhou et al. page 2723, right column and Figure 2). Furthermore, Adema et al teach that it was well known in the art that the degeneracy of the genetic code permits substitution of bases in a codon resulting in another codon still coding for the same amino acid (e.g., column 4, lines 52-56). Further, Adema et al state, "it is clear that for the expression of a polypeptide with an amino acid sequence shown in SEQ ID NO: 2 use can be

made of a derivative nucleic acid sequence with such an alternative codon composition thereby differing from the nucleic acid sequence shown in SEQ ID NO: 1" (column 4, lines 56-60). Given the knowledge of one of skill in the art with regard to the different codons that code for the same amino acid (e.g., Fomsgaard et al, Figure 7), one would have been able to readily envision all possible sequences encoding the gp100 melanoma antigen of SEQ ID NO: 2, including those with maximal GC content. Those particular variants are encompassed by the sequences taught by Adema. Thus, one of skill in the art would have a reasonable expectation of success in optimizing the codons of human melanoma antigen gp100.

The response asserts that no reasoning has been provided to explain why the evidence presented in the declaration is not commensurate in scope with the claims. Applicant is referred to page 16 of the prior Office action. The claims encompass any human tumor antigen, while the declaration tests Survivin, GP100, TRP-2, MAGE-A2, MAGE-C2 and STEP. Furthermore, the response asserts that the nature of the invention is highly unpredictable. If the nature of the invention is unpredictable, the results for the few antigens tested cannot be extrapolated to the broad class of human tumor antigens of any type of tumor. However, this is a moot point, because the results shown by the declaration are not unexpected. The declaration of Dr. Ingmar Hoerr, filed 10/14/2008, demonstrates that codon optimization increased expression of the six tumor antigens *in vivo*. Demonstration of increased expression *in vivo* by codon optimization is not unexpected, because that is the goal of codon optimization as taught in the prior art (Nagata et al, e.g., page 445, right column, full paragraph and page 450, right column, 3rd full paragraph; Fomsgaard et al page 1, lines 30-33).

The response notes that what is possible without undue experimentation and what would have been suggested by the prior art are not necessarily overlapping in scope. The Examiner agrees that the standards for enablement under 35 U.S.C. 112, first paragraph, and patentability under 35 U.S.C. 103 are distinct. However, Applicant's argument that an improved anti-tumor response *in vivo* would not have been expected is not found persuasive. The prior art specifically suggests the use of codon optimization and teaches that codon optimization is used to improve expression (e.g., Nagata et al and Fomsgaard et al). Codons are optimized for the cell type (e.g., human) in which the sequence is to be expressed and not based upon the source of the sequence (e.g., Nagata et al and Fomsgaard et al). Furthermore, Adema et al specifically teach sequences encoding human melanoma antigen gp100 that have been altered by using the degeneracy of the genetic code, which encompasses variants with maximal GC content and no rare codons. Given the combined teachings of the references cited in the rejection of record, one would have expected increased expression of the melanoma antigen gp100 protein upon codon optimization. The prior art teaches the use of codon optimization to increase expression of the encoded protein (e.g., Nagata et al, e.g., page 445, right column, full paragraph and page 450, right column, 3rd full paragraph; Fomsgaard et al page 1, lines 30-33). Thus, increased expression is not unexpected.

The response is essentially asserting that expression *in vitro* does not necessarily correlate with expression *in vivo*, and that the increased *in vivo* expression of tumor antigens such as gp100 was unexpected. However, the declaration of Dr. Ingmar Hoerr, filed 10/14/2008, does not provide comparative data with regard to *in vitro* and *in vivo* expression, where expression was unexpectedly not enhanced *in vitro* by codon optimization but was increased *in vivo*.

Demonstration of increased expression *in vivo* by codon optimization is not unexpected, because that is the goal of codon optimization as taught in the prior art (see the discussion above).

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/JD/

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